REMARKS

Claims 51, 53-59, 61-70, 82, 84-86, 88, 90, 107 and 108-109 were pending in this application. Claims 56 and 58 are being canceled herein without prejudice. Claims 53, 55, 57, 59, 62, 65-67, 84, 86, 90, 107 and 109 are being amended herein. Thus, upon entry of this Amendment and Response to Office Action, claims 51, 53-55, 57, 59, 61-70, 82, 84-86, 88, 90, 107 and 108-109 as amended will be pending. No new matter has been introduced by the amendments to the claims.

Applicant's Invention

In the October 9, 2007 Office Action the Examiner described Applicants' invention stating:

> Applicant's invention is directed to compounds and uses thereof having the formula MNOPG wherein M is an optical label or a chelator/ligand optionally complexed to a radionuclude; N, O, and P are independently absent, an alpha amino acid, a non-alpha amino acid with a cyclic group or a linking group; and G is a peptide target selected from those listed by Applicant.

In response, Applicants respectfully point out that this description is somewhat incomplete and inaccurate. Applicants note that according to the present invention N and P may be independently absent, an alpha amino acid, a non-alpha amino acid with a cyclic group and an other linking group while O is selected from an alpha amino acid or a non alpha amino acid with a cyclic group and that at least one of N, O or P may be a non-alpha amino acid with a cyclic group (or 4-aminobenzoic acid or other specific non-alpha amino acids with a cyclic group).

Non-Statutory Double Patenting Rejections

In the October 9, 2007 Office Action the Examiner rejected the pending claims under the judicially created doctrine of obviousness-type double patenting based on the claims of one issued patent and provisionally rejected the pending claims based the claims of several

pending applications. More specifically, the Examiner rejected the pending claims as being allegedly unpatentable over U.S. Patent No. 7,226,577 and provisionally rejected the pending claims based on U.S. Serial Nos. 10/542,202; 10/542,202; 11/165,721; 11/352,156; 11/467,237; 11/467,301 and 10/566,112.

In response, Applicants respectfully traverse the Examiner's double patenting and provisional double patenting rejections. Applicants respectfully request that the Examiner hold the double patenting rejection and the provisional double patenting rejections in abeyance until the Examiner specifically determines the allowable subject matter of the instant application. At such time, and if appropriate to do so, Applicants will consider submitting a terminal disclaimer.

Rejection of Claims Under 35 U.S.C. 112, second paragraph

In the October 9, 2007 Office Action the Examiner rejected claims 51, 53, 55, 57, 59, 62, 64-67, 82, 84, 86, 90, 107 and 109 under 35 U.S.C.§ 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In response, Applicants respectfully traverse the Examiner's rejections under 35 U.S.C.§112, second paragraph. Each of the Examiner's rejections will be addressed in turn below.

The Examiner rejected claims 51 and 82 alleging that the phrase "other linking group" is ambiguous. Applicants respectfully point out that this term is specifically described in the specification at, *inter alia*, paragraphs 167-171. Thus, the specification provides sufficient guidance for a person of ordinary skill in the art to understand what Applicants intend by this phrase. Moreover, Applicants note that the term "other linking group" is present in the allowed claims of U.S. Patent No. 7,226,577, which is a grandparent of the instant application.

The Examiner also rejected claim 53 based on potentially confusing nomenclature. Applicants have hereinabove amended claim 53 to remedy this potential confusion. Amended claim 53 now recites (2s, 5s)-5-amino-1,2,4,5,6,7-hexahydro-4-oxo-azepino[3,2,1-hi]indole-2-carboxylic acid, where a comma has been inserted where indicated. Accordingly, Applicants maintain that the Examiner's rejection of claim 53 is now moot.

The Examiner rejected claim 55 alleging that it is unclear what portion of the EHPG parent compound remains in the derivatives and what specific derivatives of EHPG are compatible with the instant invention. In response, while Applicants disagree with the Examiner and solely to expedite prosecution of the instant application, claim 55 has been amended to incorporate elements of claim 56 and now recites "wherein M is selected from the group consisting of EHPG, 5-Cl-EHPG, 5-Br-EHPG, 5-Me-EHPG, 5-t-Bu-EHPG, and 5-sec-Bu-EHPG." Claim 56 has been canceled. Accordingly, the Examiner's rejection of claim 55 is now moot.

The Examiner rejected claim 57 alleging that it is unclear what portion of the benzo-DTPA parent compound remains in the derivatives and what specific derivatives of benzo-DTPA are compatible with the instant invention. In response, while Applicants disagree with the Examiner and solely to expedite prosecution of the instant application, claim 57 has been amended to incorporate elements of claim 58 and now recites "wherein M is selected from the group consisting of benzodiethylenetriamine pentaacetic acid (benzo-DTPA), dibenzo-DTPA, phenyl-DTPA, diphenyl-DTPA, benzyl-DTPA, and dibenzyl DTPA." Claim 58 has been canceled. Accordingly, the Examiner's rejection of claim 57 is now moot.

The Examiner rejected claim 59 alleging that it is unclear what portion of the HBED parent compound remains in the derivatives and what specific derivatives of the HBED are compatible with the instant invention. In response, while Applicants disagree with the

Examiner and solely to expedite prosecution of the instant application, claim 59 has been amended to delete the phrase "and derivatives thereof". Accordingly, the Examiner's rejection of claim 59 is now moot.

The Examiner rejected claim 62 alleging that it is unclear what portion of the PDTA, TTHA, LICAM, and MECAM parent compounds remain in the derivatives and what specific derivatives of PDTA, TTHA, LICAM, and MECAM are compatible with the instant invention. In response, while Applicants disagree with the Examiner and solely to expedite prosecution of the instant application, claim 62 has been amended to delete the phrase "derivatives of". Accordingly, the Examiner's rejection of claim 62 is now moot.

The Examiner also rejected claim 64 alleging that it is unclear what specific compounds are compatible with the present invention. In response, Applicants maintain that a person of ordinary skill in the art would understand that any organic chromophore, organic fluorophore, light absorbing compound, light reflecting compound, light scattering compound or bioluminescent molecule which can be appended to the NOPG of the invention without destroying the ability of the compound to bind to GRP receptors may be used with the instant invention. A number of such compounds are discussed in the specification in section 1B beginning at paragraph 154 and in the section beginning at paragraph 194. Accordingly, the specification provides sufficient guidance for a person of ordinary skill in the art to understand what Applicants intend by the instant claim language.

The Examiner rejected claims 65-67 alleging that the claim did not make clear what is being imaged. In response, while Applicants disagree with the Examiner and solely to expedite prosecution of the instant application, claims 65-67 have been amended to recite "A method of imaging a subject" and the term "patient" has now been amended to refer to "subject"

so that it is consistent with the preamble of the claim. Accordingly, the Examiner's rejection of claims 65-67 are now moot.

The Examiner rejected claim 84 alleging that the original claim was unclear. While Applicants disagree with the Examiner and solely to expedite prosecution of the instant application, claim 64 has been amended recite the phrase "A method of phototherapy of a patient in need thereof...". Accordingly, Applicants believe that this amendment renders moot the Examiner's rejection of claim 84.

The Examiner also rejected claim 86 alleging that it is unclear what "other therapeutic agents" are compatible with the instant invention. While Applicants disagree with the Examiner and solely to expedite prosecution of the instant application, claim 86 has been amended to recite "...administering a chemotherapeutic on monoclonal antibody." Support for this amendment may be found in the specification, *inter alia*, at paragraph 190. Accordingly, Applicants believe that this amendment renders moot the Examiner's rejection of claim 86.

The Examiner rejected claim 90 alleging that as originally presented the claim was unclear. While Applicants disagree with the Examiner and solely to expedite prosecution of the instant application, claim 90 has been amended to recite the phrase "and P is absent." Accordingly, Applicants believe that this amendment renders moot the Examiner's rejection of claim 90.

The Examiner rejected claims 107 and 109 for not terminating with a period. In response, Applicants have amended claims 107 and 109 such that each claim terminates with a period. Accordingly, the rejection of these claims is now moot.

For the foregoing reasons, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. § 112.

Rejection of Claims Under 35 U.S.C. § 103(a)

In the October 9, 2007 Office Action the Examiner rejected claims 51, 54-62, 64-70, 88 and 108 under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 7,147,838 (hereinafter "Hoffman") in view of Nuclear Medicine and Biology, 2002, Vol. 29, pp 423-430 (hereinafter "Hu") and J. Med. Chem. 2002, Vol. 545 pp 2003-2015 (hereinafter "Achilefu"). The Examiner asserted that both Hoffman and Applicant disclose compounds encompassed by Applicant's formula MNOPG.

In response, Applicants respectfully traverse the Examiner's rejection under 35 U.S.C. § 103(a). At the outset, Applicants point out that while Hoffman may describe bombesin (8-14) as a preferred peptide, Hoffman is completely silent with respect to the claimed derivatives of bombesin (7-14) and the other claimed targeting peptides as well as these targeting peptides in combination with a spacer and a metal moiety. Applicants note that Hoffman's preferred peptide differs by one amino acid residue, glutamine (Q) and the terminal –OH group, from that of Applicant's SEQ No. 1.

As pointed out above, Applicants' claims recite a linking group NOP in which N and P are independently absent, an alpha amino acid, a non-alpha amino acid with a cyclic group or an other linking group, while O is selected from an alpha amino acid or a non alpha amino acid with a cyclic group and the claims require that at least one of N, O or P is a non-alpha amino acid with a cyclic group (or a specific non-alpha amino acid with a cyclic group such as 4-aminobenzoic acid). Hoffman does not disclose, teach or suggest such linkers. Indeed, Hoffman teaches that the linkers (which he also calls spacer groups) "can include a peptide (i.e., $\geq$ 1 amino acid in length), a hydrocarbon spacer of C1-C10 or a combination thereof." (See Col 5, lines 48-50, see also Col 5, line 60-Col 6, line 17.) Hoffman's preferred linkers consist of a Glu residue followed by attachment of FmOC protected terminal amine groups separated from a –COOH

group by 3-, 4-, 5-, 6-, 8- and 11-carbon chain (CH) spacers. (See Example 1, Col 10, lines 39-46.) These linkers do not include a non-alpha amino acid with a cyclic group as recited in the instant claims.

Indeed, Hoffman does not disclose, teach or suggest in any way non-alpha amino acids with cyclic groups.[1] Importantly, as shown in examples LIII, LV, LX and LXI of the instant application, the cyclic non-alpha amino acid linkers of the instant invention have unexpectedly superior properties compared to the linkers described by Hoffman. For instance, Example LIII compares a representative compound having a linker according to the present invention (L70 – DO3A monoamide-Gly-4-aminobenzoic acid-QWAVGHLM-NH2) with a compound with a Hoffman linker, DO3A monomaide-Aoc-QWAVGHLM-NH2. The linker, Aoc is 8-aminooctanoic acid and is one of Hoffman's preferred linkers (see, e.g. in BBN-44 in Figure 6B it is attached to BBN(8-14), and in BBN-47 in Figure 9 it is further attached to a chelator). Example LIII of the instant application shows that representative compounds of the present invention have higher uptake in tumor tissue than compounds described using linkers preferred by Hoffman.

Similarly, in Example LV of the instant application, a representative compound of the present invention, L70, exhibits increased survival in a rodent radiotherapy experiment over the compound with Hoffman's preferred linker, DO3A monomaide-Aoc-QWAVGHLM-NH2. In addition, Examples LX and LXI show that representative compounds of the present invention with linkers including a non-alpha amino acid containing a cyclic group have superior properties to compounds without these linkers.

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[1] Note that contrary to the Examiner's assertions (OA at p. 13), histidine, phenylalanine, tyrosine and tryptophan are not non-alpha amino acids with a cyclic group as recited in Applicant's claims. Indeed, these are alpha amino acids which, unlike non-alpha amino acids, have the -COOH and -NH_2 groups both attached to the same carbon atom, called the alpha carbon atom.

Further, Hoffman does not disclose the GRP targeting peptides recited in the claims. As the Examiner acknowledges, Hoffman discloses BBN(8-14) which is WAVGHLM. In contrast, the instant claims recite derivatives of BBN(7-14) and other GRP receptor binding moieties which, despite their modifications from the known GRP receptor binding moiety, were found to bind to GRP receptors when included in compounds of the invention. (See e.g. Table 4 and Example LXI.) Hoffman does not disclose, teach or suggest these modifications, let alone that compounds including such modified peptides would retain the ability to bind GRP receptors.

In sum, (1) Hoffman does not disclose teach or suggest compositions according to the instant invention; (2) compositions of the present invention exhibit unexpectedly superior properties as compared to Hoffman; and (3) given Hoffman's preference for specific compositions having inferior properties compared to the composition claimed by Applicants, Hoffman affirmatively teaches away from Applicants' claimed invention.

The secondary references cited by the Examiner do not remedy Hoffman's deficiencies. Neither Hu nor Achilefu discloses, teaches or suggests the linkers or even many of the targeting peptide derivatives claimed by Applicants. Indeed, Hu describes just two compounds. The first, DO3A-amide-BBN, includes the chelator DO3A linked directly to the targeting peptide BBN(7-14)NH2, with no linker. The second, DO3A-amide-βAla-BBN, includes the chelator DO3A linked to the targeting peptide BBN(7-14)NH2, via a βAla linker. Use of a linker of the invention, including a non-alpha amino acid with a cyclic group is not disclosed, taught or suggested by Hu, nor are the vast majority of the claimed targeting peptides.

Likewise, Achilefu fails to cure the deficiencies of Hoffman alone or in combination with Hu. Achilefu merely describes conjugates of bombesin derivatives with optical imaging agents and/or chelators. Importantly Achilefu fails to disclose, teach or suggest the use of linkers according to the present invention, wherein such linkers include a non-alpha

amino acid with a cyclic group and wherein the use of such linkers provide significantly advantageous properties over compositions described by other references.

Therefore, since the secondary references do not cure the deficiencies of Hoffman, these references taken together or separately cannot render obvious the presently pending claims. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 103(a).

In view of the foregoing, Applicants respectfully submit that the presently pending claims are in condition for allowance. If a telephone interview would be of assistance in advancing prosecution of this application, Applicant's undersigned attorney encourages the Examiner to telephone him at the number provided below.

No fee is believed to be necessary in connection with the filing of this Amendment and Response to Office Action. If any additional fee is necessary, however, applicant hereby authorizes such fee to be charged to Deposit Account No. 50-0540.

Respectfully submitted,

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